Pilot study: postoperative pain reduction by pre emptive N-Acetylcysteine

Published: 10-07-2017
Last updated: 14-04-2024

Primary Objective: To evaluate the efficacy of intravenous NAC in comparison with placebo in terms of pain relief after unilateral inguinal hernia repair measured by a visual analogue scale (VAS 0-100) at day 1 after surgery.Secondary Objective(s):...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON45293

Source
ToetsingOnline

Brief title
NAC.TEP16

Condition

- Other condition

Synonym
postoperative pain after inguinal hernia repair

Health condition

Pijngeneeskunde

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: inguinal hernia, N-Acetylcysteïne, pain, postoperative

Outcome measures

Primary outcome

Primary objective is to evaluate the efficacy of intravenous NAC in comparison with placebo in terms of pain relief after unilateral inguinal hernia repair measured by a visual analogue scale (VAS 0-100) at day 1 after surgery.

Secondary outcome

* Pain scores (VAS 1-100) direct postoperatively , before discharge and in following 3 days postoperative.

* Time to first necessity of pain medication after surgery (in minutes).

* Total consumption of in hospital opiates (in mg).

* Time to discharge (in minutes).

* Analgesic medication taken at home by patient (registered by patients in diary) (in mg).

* Adverse effect of analgesic medication (nausea, obstipation, sedation) (in numbers).

Study description

Background summary

Currently approximately 240 million surgical procedures are done worldwide on a

yearly basis. Inguinal hernia repair is one of the most performed surgeries in ambulatory setting. Despite currently available analgesic drugs, post surgical pain management remains challenging in this group of patients, as the pain score appears inadequate (mean VAS of 5.8 +/- 1.22 cm) one day after surgery with the use of common analgesics. Beside accounting for patient discomfort, pain is also a major contributor to prolonged length of hospital stay and is a health care quality indicator.
With multimodal pain management the intention is to reduce pain with less side effects of analgesics. Multimodal pain management is the combination of different pharmacologic mechanisms of action, which work by acting at different sites within the central and peripheral nervous system, thereby having an additive or synergistic effect and reducing the necessity of opiates.
With this in mind, a potential new target for analgesic drugs are group- II metabotropic glutamate receptors subtypes (mGlu2 and mGlu3 receptors) localized in the spinal cord and other regions of the nociceptive system. Growing evidence from animal models show that activation of these receptors occur via the glutamate:cystein antiporter and can induce analgesia in models of inflammatory and neuropathic pain. They depress pain transmission at synapses between primary afferent fibers and second order sensory neurons on the dorsal horn of the spinal cord.
N-Acetylcysteine (NAC) is on the market since 1968 and is an over the counter available agent, mostly known for its role as mucolytic agent in cystic fibrosis and for the treatment of acetaminophen intoxication. It is a safe agent with little to no side effects. Recent studies have shown NAC can inhibit nociceptive transmission in rats and in healthy humans.NAC can induce analgesia by activating the glutamate:cystein antiporter, causing endogenous activation of the mGlu2/3 receptors.
Therefore, NAC can potentially become a cheap and safe additive in the multimodal pain management. However, evidence for usage of NAC in the context of multimodal pain management is still lacking. Only one available study in humans evaluated the effect of NAC in the perioperative setting. Despite being a randomised controlled trial, there are several limitations in this study; the study arms are too small and only morphine consumption is presented. Also, blinding might have not as good as suggested since oral NAC has a typical flavour and the placebo was lemonade. Due to these limitations, still no answer on the question whether NAC can be an additive in current multimodal painmanagement is provided.

Study objective

Primary Objective:
To evaluate the efficacy of intravenous NAC in comparison with placebo in terms of pain relief after unilateral inguinal hernia repair measured by a visual analogue scale (VAS 0-100) at day 1 after surgery.

Secondary Objective(s):
1. Difference in pain scores between NAC and placebo direct after surgery,

before discharge and in following 3 days postoperative.
2. Difference in time before first pain medication is administered postoperative between NAC and placebo.
3. Difference in total consumption of opiates in the hospital (mg) between NAC and placebo.
4. Difference in time from surgery to discharge between NAC and placebo.
5. Difference in postoperative pain medication at home necessary to reach adequate pain relief between NAC and placebo (Acetaminophen /NSAID*s/opiates).
6. If there is a difference in 5, is there also a difference in adverse effects of pain medication (like nausea, obstipation) between NAC and placebo.

Study design

The study will be a single centre double blinded randomized placebo controlled trial

Intervention

The following NAC infusion regimen will be conducted. One hour prior to surgery, the patients will receive 150 mg/kg in 200 ml intravenous bolus over 15 minutes. During NAC infusion, patients vital signs will be adequately monitored.

Patients who are not included in the treatment arm of the study will receive intravenous saline instead with identical look of NAC in the same timeframe and dosage (200ml).

Study burden and risks

Patients will need to be admitted earlier in the hospital prior to surgery, to make sure they receive study medication in time.
An intravenous line will be placed on the ward to be able to administer study medication, however, this same line can be used during and after surgery.
During administration of the study medication subjects will be monitored respiratory and hemodynamically, to ensure possible side effects of NAC are captured.
Oral NAC is safe agent and even over the counter available in the Netherlands. Subjects will have little extra risks due to the intravenous NAC given in this concentration. The main risk is the occurrence an anaphylactoid reaction, which is easily treated by antihistaminic and seldom described as serious in the literature. [1-5] Careful monitoring of subjects will ensure any potential side effect or adverse event are noticed and treated as quickly as possible.
After discharge patient receive a diary and will record: 1) VAS at predetermined time, 2) pain medication used, 3) side effects of pain medication (nausea, obstipation, dizziness) and 4) overall satisfaction.
Total time investment of participants should not exceed more than 2 hours in

total.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

subjects ASA 1-2 sceduled for laparoscopic inguinal hernia repair

Exclusion criteria

- Pregnancy or lactating
- Allergy to NAC
- History of chronic pain

- Use of opioids or neuropathic analgesics
- Use of NAC prior to trial (< 1 month of planned surgery)
- Alcoholism
- Diabetes Mellitus
- Asthma or Chronic Obstructive Pulmonary Disease
- Known renal function disorders (MDRD <60)
- Known liver failure (bilirubine >1.5x upper limit of normal)
- No written IC by patient

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-11-2017
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Fluimucil
Generic name:	N-Acetylcysteine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-07-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-11-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-003144-36-NL
CCMO	NL58787.091.16

Study results

Date completed:	29-10-2018
Actual enrolment:	60